Docket No.: IBIS-0339
Title: GENERATION OF VIRTUAL COMBINATORIAL
LIBRARIES OF COMPOUNDS
Inventors: Richard Griffey and Eric Swayze
Atty: Paul K. Legaard - Telephone: 215 568 3100

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Compound CI

$$C_{12}H_{18}N_2O_5S$$

	F_i	F_{ii}	F_{iii}
Molecular formula	H_2NO	C_5H_9NO	$C_7H_7O_3S$

Figure 1

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Addition of fragments to yield compounds
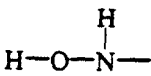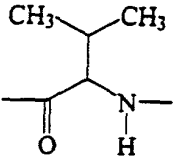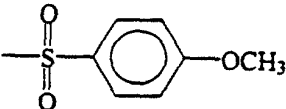
Table

Fragment Identifier	Structure	Name	Molecular formula	Other
F_i		Hydroxylamine	H_2NO	...
F_{ii}		Amino acid	C_5H_9NO	...
F_{iii}		Sulfonyl	$C_7H_7O_3S$	...

Figure 2

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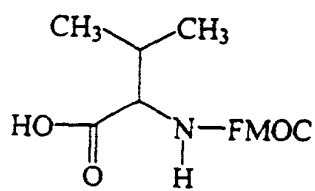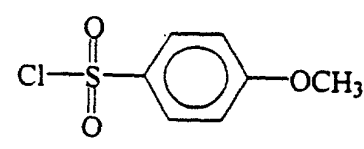
Reagents	Identifier	Name	Properties
$H-O-NH_2$ or $\textcircled{P}-O-NH_2$	R_i	Hydroxylamine	...
[FMOC blocked amino acid structure]	R_{ii}	FMOC blocked amino acid	...
[Sulfonylchloride structure]	R_{iii}	Sulfonylchloride	...

$\textcircled{P}$ = Solid support

Figure 3

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Transformation

T_i Reagent R_i

reaction conditions alpha

Fragment F_i

T_{ii} Reagent R_{ii}

reaction conditions beta

Fragment F_{ii}

T_{iii} Reagent R_{iii}

reaction conditions gamma

Fragment F_{iii}

(P) = Solid support

Figure 4

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Common Fragment / Different Reagents and Transformations

Reagent X

Transformation A

Common Product Fragment

Transformation B

Reagent Y

Figure 5

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Common Fragment / Different Reagents and Transformations

$$CH_3CH_2-N=\overset{\overset{\displaystyle H}{|}}{C}-$$

↑ Transformation X

Common reagent Z $CH_3CH_2-NH_2$

↓ Transformation Y

$$CH_3CH_2-NH-\overset{\overset{\displaystyle O}{\|}}{C}-$$

Figure 6a

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Common Reagent

CH_3 —— CH ~~~

↑   Transformation X'

Common reagent Z' CH_3 —— CH_2 ~~~ (with O)

↓   Transformation Y'

CH_3 —— CH_2 ~~~ (with OH)

Figure 6b

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Symbolic addition of fragments to yield compound
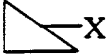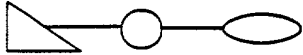
Symbolic Structure	Symbolic Identifier	Molecular formula

Fragment

 $F_{i'}$ $C_u H_v N_w \ldots$

 $F_{ii'}$ $C_u H_v N_w \ldots$

 $F_{iii'}$ $C_u H_v N_w \ldots$

Compound

 CI' $C_u H_v N_w \ldots$

$$\begin{array}{c} \text{Molecular formula } F_{i'} \\ + \\ \text{Molecular formula } F_{ii'} \\ + \\ \underline{\text{Molecular formula } F_{iii'}} \\ = \text{Molecular formula } CI' \end{array}$$

Figure 7

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Symbolic Reagent Table
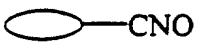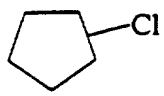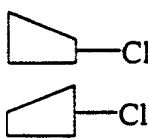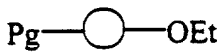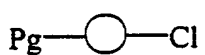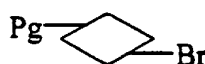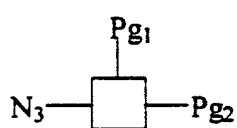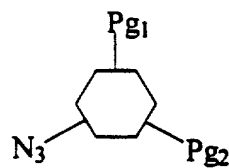
Identifier	Name	Structure	Molecular formula
R1	xxx	▷—Cl	xxx
R2	...	⬭—CNO	...
R3	...	(pentagon)—Cl	...
R4	...	(pentagon)—Br	...
R5	...	(trapezoid)—Cl (trapezoid)—Cl	...
R6	...	Pg—◯—OEt	...
R7	...	Pg—◯—Cl	...
R8	...	Pg—◇—Br	...
R9	...	N_3—▢—Pg_2 with Pg_1	...
R10	...	N_3—⬡—Pg_2 with Pg_1	...

Figure 8

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Symbolic Fragment Table
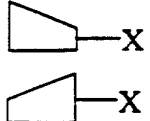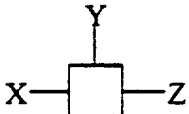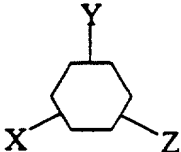
Identifier	Symbolic Structure	Molecular formula	Molecular Weight
F1	▱—X	xxx	xxx
F2	⬭—X	...	...
F3	⬠—X	...	...
F4	▱—X ◸—X	...	...
F5	X—◯—Y	...	...
F6	X⬦Y	...	...
F7	X—▢—Z (Y above)	...	...
F8	X—⬡—Z (Y above)	...	...

Figure 9

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Symbolic Transformation Table
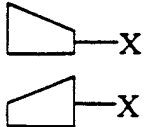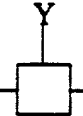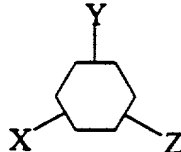
Identifier		Symbolic Reactions	Reagent

T1	F1	◁—X ⟵ R1	conditions α
T2	F2	⬭—X ⟵ R2	conditions β
T3	F3	⬠—X ⟵ R3	conditions α
T4	F3	⬠—X ⟵ R4	conditions α
T5	F4	⬓—X / ⬓—X ⟵ R5	conditions α
T6	F5	X—◯—Y ⟵ R6	conditions ε
T7	F5	X—◯—Y ⟵ R7	conditions α
T8	F6	X—◇—Y ⟵ R8	conditions α
T9	F7	X—▢—Z (Y top) ⟵ R9	conditions γ
T10	F8	⬡ (Y top, X and Z bottom) ⟵ R10	conditions γ

Figure 10

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Single Compounds and Mixtures
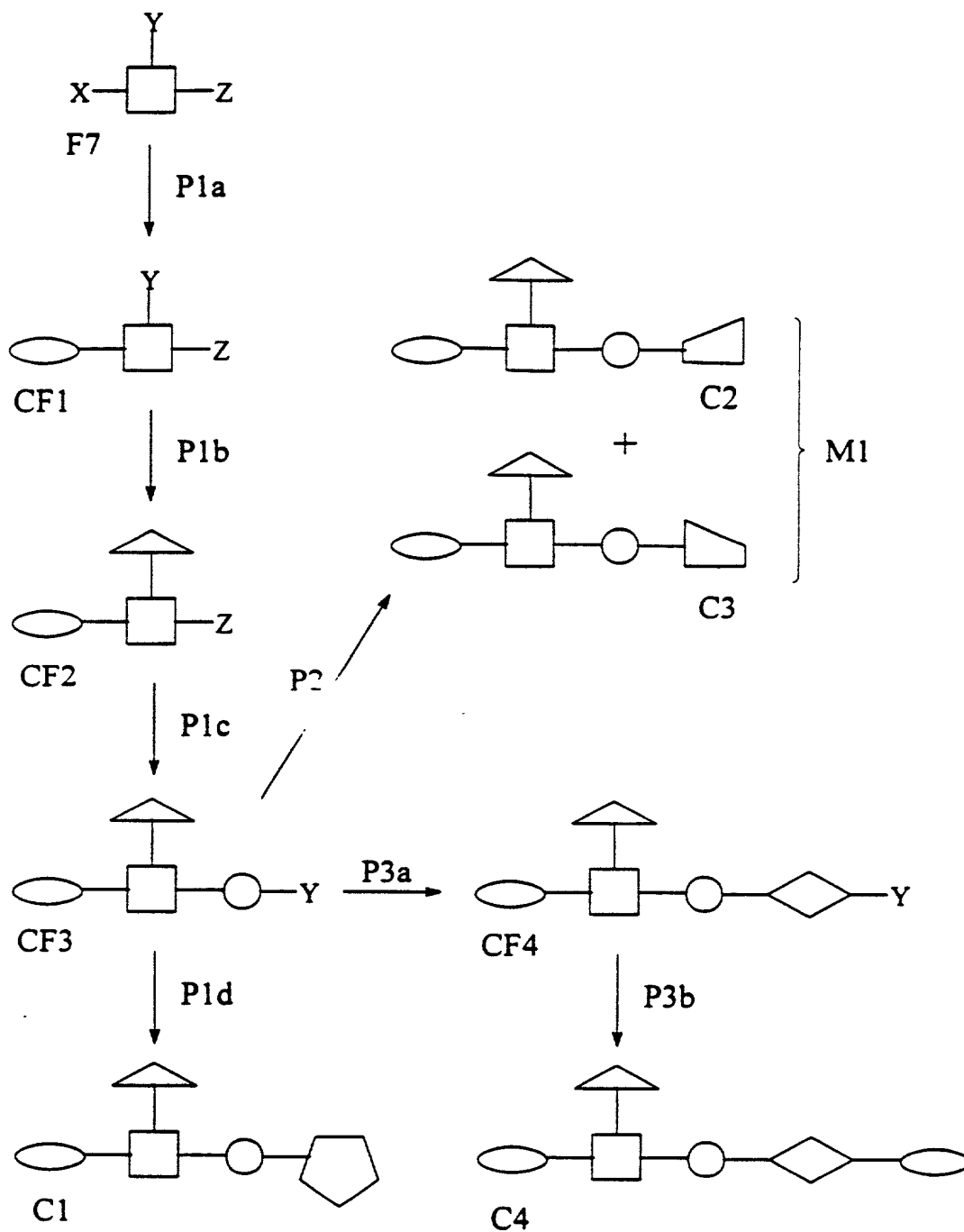
P = synthetic path   CF = complex fragment
F = fragment   M = mixture
C = compound

Figure 11

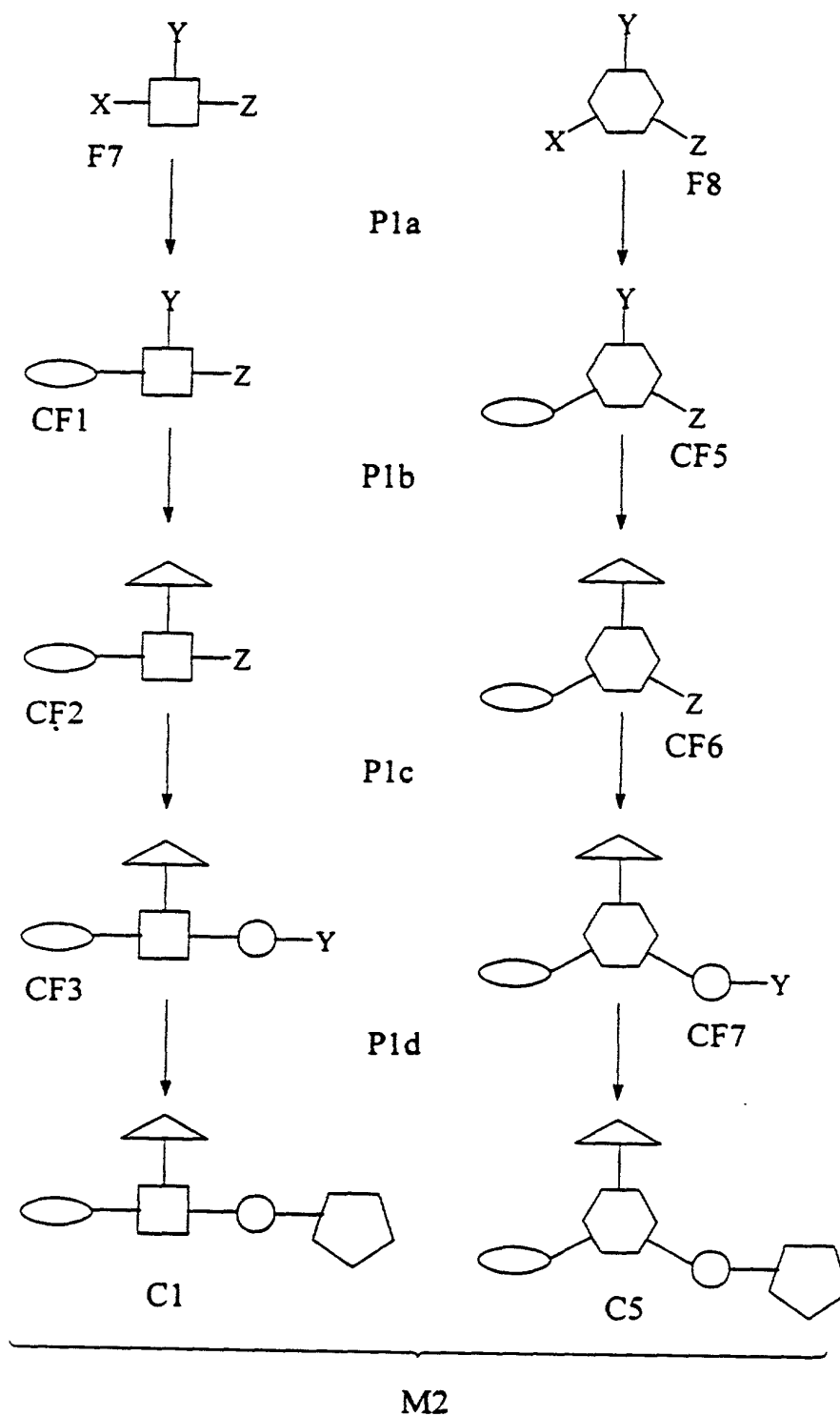Docket No.: IBIS-0339
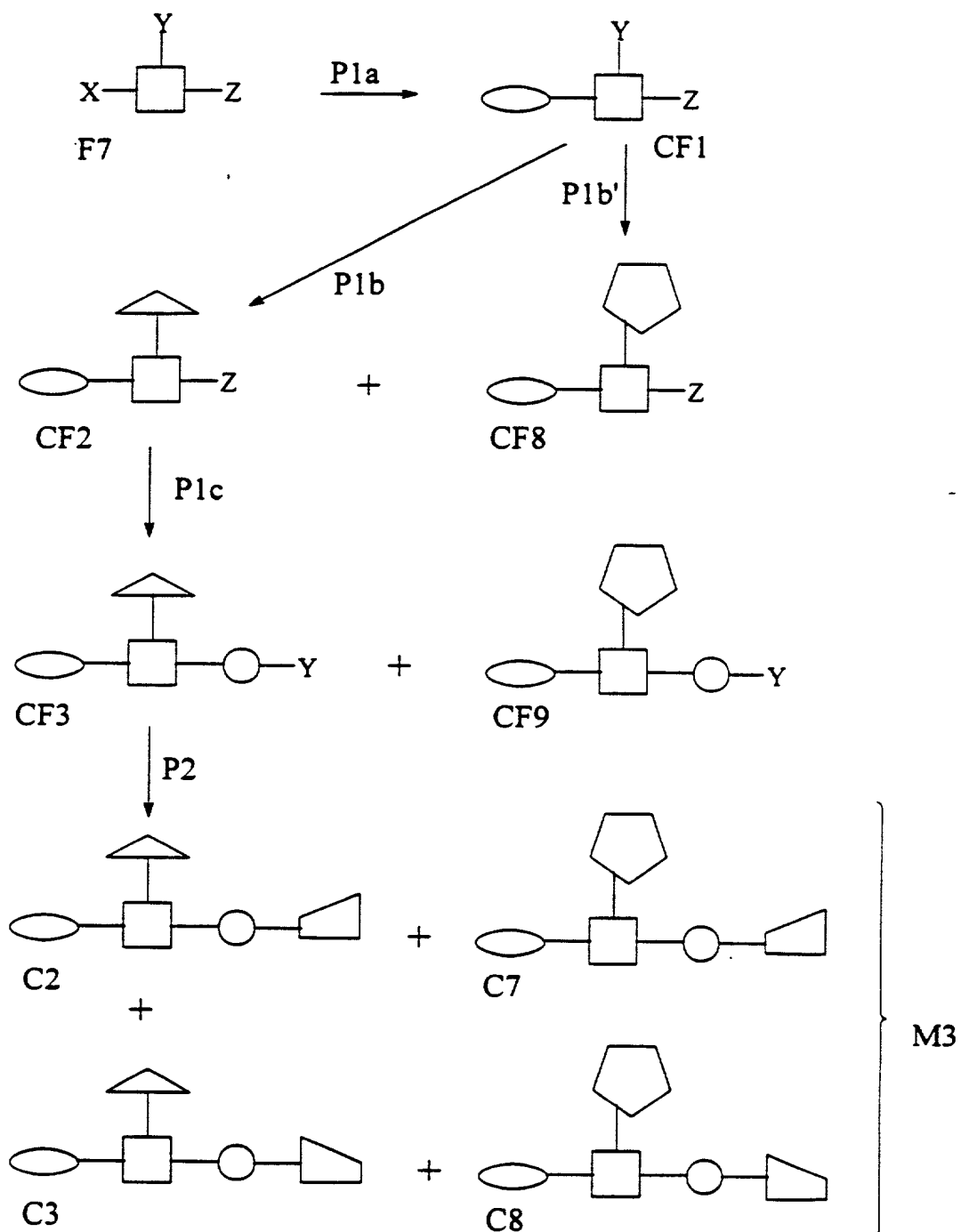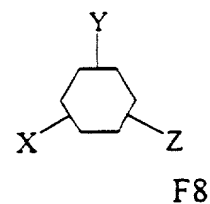Title: GENERATION OF VIRTUAL COMBINATORIAL
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Mixture 2

Figure 12

Mixture 3

Figure 13

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Mixture 4

2 Starting Fragments
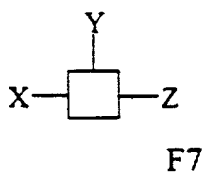
F7

F8

2 Complex Fragments

CF1

CF5

4 Complex Fragments

CF2

CF8

CF 6

CF11

8 Complex Fragments

CF3

CF9

CF12

CF13

CF15

CF16

CF 7

CF14

Figure 14a

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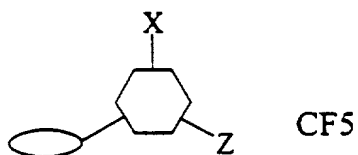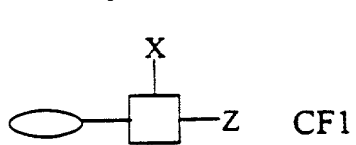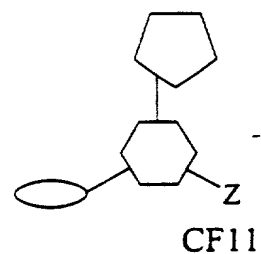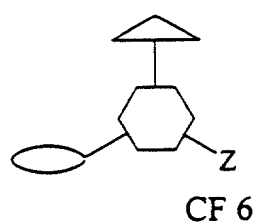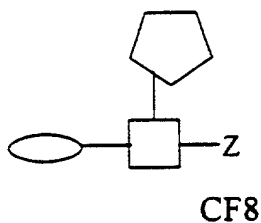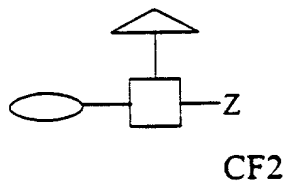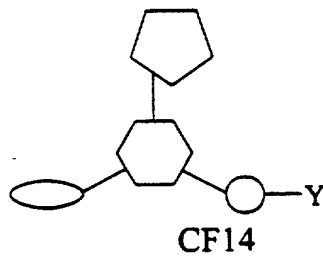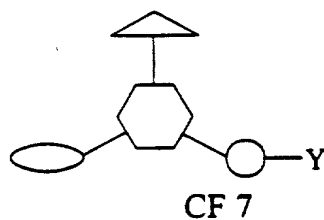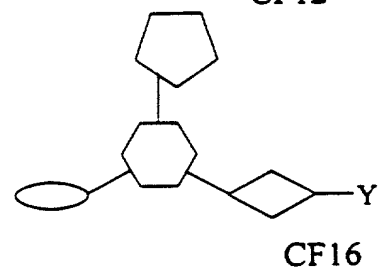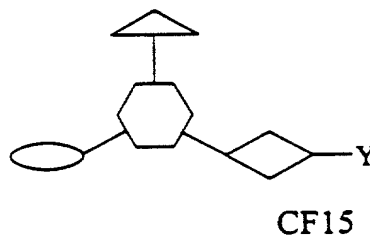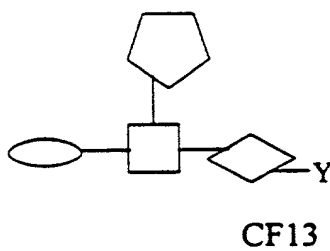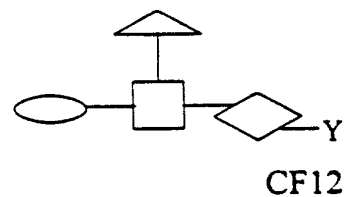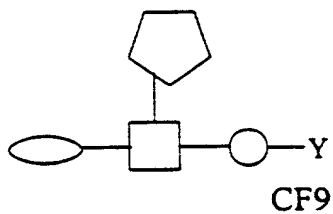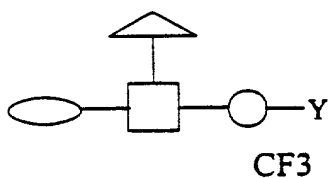
Mixture 4 (continued)

16 compounds

C3   C8   C10

C2   C7   C9

C12   C18   C20

C11   C17   C19

C14   C16   C15

C13

Figure 14b

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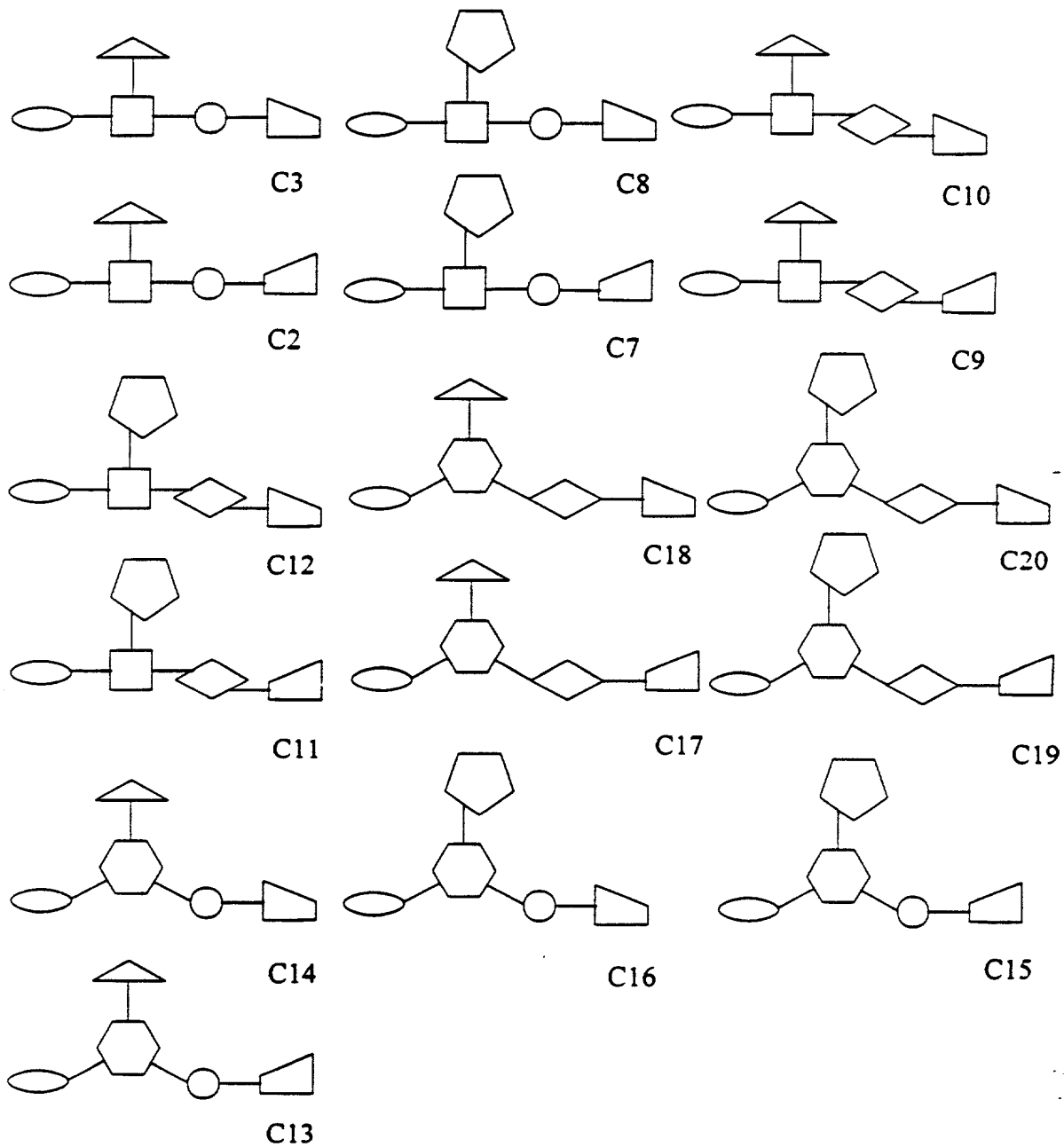
Tracking Table for Compound C1

(a) By Fragments:

```
n       n+1      n+2
F7 |
   |    F2
   |    F1
   |    F5
   |        |
   |        |    F3
```

(b) By Transformations:

Synthesis Path 1

```
n       n+1      n+2
T9 |
   |    T2
   |    T1
   |    T6
   |        |
   |        |    T3
```

Synthesis Path 2

```
n       n+1      n+2
T9 |
   |    T2
   |    T1
   |    T7
   |        |
   |        |    T3
```

Synthesis Path 3

```
n       n+1      n+2
T9 |
   |    T2
   |    T1
   |    T6
   |        |
   |        |    T4
```

Synthesis Path 4

```
n       n+1      n+2
T9 |
   |    T2
   |    T1
   |    T7
   |        |
   |        |    T4
```

Figure 15

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Tracking Table

Tracking M1

Step 1

T9

Step 2

T9   T2

Step 3

T9   T2
     T1

Step 4

T9   T2
     T1
     T7

Step 5

T9   T2
     T1
     T7
        $T5^1$

C2

Step 5

T9   T2
     T1
     T7
        $T5^2$

C3

Figure 16

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Tracking Table

Tracking M2

Step 1

n	n+1	n+2
T9		

Step 1

n	n+1	n+2
T10		

Step 2

n	n+1	n+2
T9	T2	

Step 2

n	n+1	n+2
T10	T2	

Step 3

n	n+1	n+2
T9	T2	
	T1	

Step 3

n	n+1	n+2
T10	T2	
	T1	

Step 4

n	n+1	n+2
T9	T2	
	T1	
	T7	

Step 4

n	n+1	n+2
T10	T2	
	T1	
	T7	

Step 5

n	n+1	n+2
T9	T2	
	T1	
	T7	
		T4

C1

Step 5

n	n+1	n+2
T10	T2	
	T1	
	T7	
		T4

C5

Figure 17

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Tracking Table

Tracking M3

Figure 18